ORIGINAL ARTICLE

Varicella vaccination in England and Wales: cost-utility analysis

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Aims: To assess the cost-effectiveness of varicella vaccination, taking into account its impact on zoster.
Methods: An age structured transmission dynamic model was used to predict the future incidence of varicella and zoster. Data from national and sentinel surveillance systems were used to estimate age specific physician consultation, hospitalisation, and mortality rates. Unit costs, taken from standard sources, were applied to the predicted health outcomes.
Results: In England and Wales, the annual burden of VZV related disease is substantial, with an estimated 651 000 cases of varicella and 189 000 cases of zoster, resulting in approximately 18 000 QALYs lost. The model predicts that although the overall burden of varicella will significantly be reduced following mass infant vaccination, these benefits will be offset by a significant rise in zoster morbidity. Under base case assumptions, infant vaccination is estimated to produce an overall loss of 54 000 discounted QALYs over 80 years and to result in a net cost from the health provider (NHS) and the societal perspectives. These results rest heavily on the impact of vaccination on zoster. Adolescent vaccination is estimated to cost approximately £18 000 per QALY gained from the NHS perspective.
Conclusion: Routine infant varicella vaccination is unlikely to be cost-effective and may produce an increase in overall morbidity. Adolescent vaccination is the safest and most cost-effective strategy, but has the least overall impact on varicella.

The introduction of universal varicella vaccination in the USA has stimulated intense interest in varicella vaccination elsewhere. There have been many cost-effectiveness analyses of varicella vaccination, but all have concentrated on the effect of vaccination on varicella.[1–6] However, varicella zoster virus (VZV) infection causes two diseases: varicella after initial infection and zoster following reactivation. It has long been recognised that exposure to varicella might reduce the risk of reactivation (zoster) by boosting specific immunity to VZV.[7] Two recent epidemiological studies have shown that this mechanism plays an important role in protection against zoster.[8 9] Mathematical modelling based on these results predicts that, by reducing circulating VZV, universal varicella vaccination will lead to a significant increase in zoster, which can last up to 50 years.[9–11] These findings support a re-evaluation of varicella vaccination, taking into consideration its impact on zoster. Here, we estimate, for the first time, the cost-utility of varicella vaccination, taking account of the impact of varicella vaccination on all VZV associated disease.

METHODS

Model and methodological assumptions

We compare three different vaccination strategies to no vaccination. The strategies are:

(1) *Infant strategy*: routine mass infant vaccination at 90% coverage.

(2) *Catch-up strategy*: infant strategy with catch-up (at 80% coverage) targeted at susceptible 2–11 year olds in the first year.

(3) *Adolescent strategy*: routine vaccination of 11 year old susceptibles (at 80% coverage).

We used a realistic age structured (RAS) transmission dynamic model to predict the impact of vaccination on varicella and zoster.[10] The average period of boosting following exposure to VZV was taken from Brisson and colleagues,[9] and all other epidemiological parameter values were taken from

Brisson and colleagues[11] unless otherwise stated. The model can capture herd immunity effects, including post-immunisation shifts in the age at infection.

We performed the economic analysis from the perspective of the health care provider (NHS) and of society. The primary viewpoint is that of the health care provider because data from this perspective are more complete for the UK. This perspective includes all direct medical costs including physician contacts, hospitalisations, and prescription medications. The societal perspective includes all medical and work loss costs as well as household expenditures. Future costs and outcomes are discounted at 3% per year. In the sensitivity analysis, results are presented using alternative discount rates. Costs and benefits are presented over an 80 year time horizon. We chose cost and cost-utility analysis (cost per quality adjusted life year (QALY) saved) as analytical techniques.

Vaccine efficacy and epidemiological estimates

We estimated vaccine efficacy parameters values by fitting the predicted number of breakthrough infections (cases in seroconverted vaccinees) with observed data in clinical trials.[10] The base, best, and worst case vaccine efficacy parameter values are presented in Brisson and colleagues.[10]

We estimated the predicted number of cases of natural and breakthrough varicella, and zoster directly from the model. The estimated age specific proportion of physician consultations, hospital length of stay, and deaths per case of varicella and zoster were applied to the predicted number of cases by age and time.

The age specific number of episodes of varicella and zoster which result in a consultation with a general practitioner (GP) and the average (age specific) number of consultations per episode were taken from the Royal College of General Practitioners (RCGP) Weekly Returns Service data for 1991–2000.[12]

Table 1 Health outcome estimates

Parameters	All	0–4	5–14	15–44	45–64	65+	Source*
% cases consult GP							
Natural varicella		45%	45%	72%	82%	100%	[12]
Breakthrough varicella		45%	45%	72%	82%	100%	[12,13]
Zoster		100%	100%	100%	100%	100%	[12]
Number of visits per consultation							
Natural varicella		1.18	1.24	1.29	1.40	1.43	[12]
Breakthrough varicella		1.00	1.00	1.00	1.00	1.00	Assumption
Zoster		1.07	1.18	1.36	1.43	1.68	[12]
Hospitalisations per case							
Natural varicella		0.37%	0.14%	0.62%	1.38%	3.14%	[12]
Breakthrough varicella		0.07%	0.03%	0.12%	0.28%	0.63%	[12,14]
Zoster		1.12%	0.66%	0.50%	0.60%	2.28%	[12]
Length of stay							
Natural varicella		2.22	2.96	3.97	5.77	10.57	[12]
Breakthrough varicella		2.22	2.96	3.97	5.77	10.57	[12]
Zoster		3.53	3.35	4.58	5.23	13.54	[12]
Case fatality							
Natural varicella		0.001%	0.001%	0.009%	0.073%	0.689%	[12]
Zoster		0.000%	0.001%	0.002%	0.002%	0.061%	[12]
VZIG per case		0.2%	0.2%	3.3%	0.2%	0.2%	PHLS
PHN per zoster case		0%	1%	4%	11%	31%	[17]
Duration of PHN (days)	511						[17]
QALY lost per case							
Natural varicella		0.004	0.004	0.005	0.005	0.005	See methods
Breakthrough varicella		0.001	0.001	0.001	0.001	0.001	Assumption
Zoster	0.010						[17]
PHN	0.462						[17]

*Reference numbers in square brackets.
VZIG, varicella zoster immune globulin; PHN, post-herpetic neuralgia.

Age specific hospitalisation rates and length of stay data were taken from the Hospital Episodes Statistics (HES, Department of Health) for 1995–96, which covers the whole of England (numbers were multiplied up by the additional population size to include Wales).[12] Based on Office of National Statistics (ONS) death certificates, the average number of deaths in England and Wales attributed to chickenpox and herpes zoster over the period 1993–2000 were used to calculate age specific case fatality ratios.[12]

Breakthrough cases were assumed to visit a physician at the same rate as natural varicella cases,[13] to have a fivefold lower risk of hospitalisation,[14] and not to result in death. We excluded adverse events from our analysis since they are rare,[15] and thus would not contribute significantly to the overall burden of the vaccine.

The age specific population size was taken from the Office for National Statistics (ONS) estimates for mid-1998.[16] We used the population distribution of mid-1998 and assumed that the birth and death rates will remain constant in the future.

Outcome measures
Table 1 presents the QALYs lost due to varicella and zoster. QALYs lost due to zoster were taken from Edmunds and colleagues.[17] To estimate the QALY lost due to varicella in children, parents were recruited from health clinics in London at the time of routine infant and child check-ups. Parents were approached in the waiting room where they were given an information leaflet and asked to participate in the study. Those consenting were asked to rate the health state of a child with chickenpox using an existing generic health status index (Health Utilities Index mark 2, HUI2). Only parents of children with prior history of chickenpox (n=42) are reported in this study (further details of the study will be published elsewhere). The HUI2 was chosen because it was developed for childhood diseases using parents as proxies. The quality of life weighting of adults with chickenpox was assumed to be similar to that of mild zoster. To assess QALYs lost, varicella was assumed to have an average duration of seven days. An extensive sensitivity analysis was performed for these estimates.

Cost data and assumptions
Unit costs are in Sterling equivalent in 2001 (£1 = US$1.5 or €1.5) and shown in table 2. Costs estimated in previous years are inflated to 2001 values by the use of the Hospital and Community Health Services (HCHS) Pay and Prices Index.[18]

Direct costs
The average cost per inpatient day and the average cost per GP consultation were taken from Unit Costs of Health and Social Care.[19] Varicella zoster immunoglobulin (VZIG) in England and Wales is administered by the Public Health Laboratory Service (PHLS). Data from 2000 were used to estimate the average number of VZIG doses administered annually: 5426. Pregnant women given VZIG (4166 vials) were assumed to be aged 15–44 years. Each vial of VZIG costs £240.

Wreghitt et al estimated the cost of infection control measures for a sample of 70 hospitalised patients with either varicella or zoster.[20] Measures included serological diagnosis, staff exclusion, the use of VZIG and antiviral drugs, and patient isolation. We assume that these measures result in an average fixed cost associated with each hospitalised patient (that is, independent of their length of stay). Excluding the cost of administration of VZIG (to avoid double counting) this amounts to £722 per varicella hospitalisation, two thirds of which is due to staff exclusion. In all analyses it is assumed that contact with a breakthrough case by an at-risk susceptible would be as likely to result in the use of VZIG as contact with natural varicella.

The 1998 Prescription Cost Analysis for England[21] was used to estimate the cost of community prescribed drugs for treatment of varicella and zoster (the cost of hospital prescriptions being included in the study by Wreghitt and colleagues[20]) using assumptions described by Edmunds and colleagues.[17] The average prescription cost per consultation for varicella and zoster is estimated to be £2 and £35 respectively.

In our base case analysis, we assumed the vaccine costs £30 per course (varied in the sensitivity analysis). For the *infant* strategy, we assume that varicella vaccination will be administered concurrently with MMR at 12–15 months, and therefore will not incur additional costs such as practice nurse

Table 2 Cost estimates (£)

Parameters	All	Natural varicella	Breakthrough varicella	Zoster	Source*
Vaccination costs					
Cost of vaccine course	30				Assumption
Extra cost per course for adolescent and catch-up	10				Assumption
Self reported history of chickenpox					
Sensitivity	97%				[3]
Specificity	70%				[3]
Direct costs					
Cost GP consult		22	22	22	[19]
Treat cost GP consult		2	–	35	[21]
Cost inpatient day		219	219	219	[19]
Average treat cost hospitalisation		722	722	875	[20]
Cost per dose of VZIG		240			PHLS†
Indirect costs					
Not hospitalised					
Work days lost per case					
0–15		0.6	0.6	10	[3,5,23]
16+		5.7	5.7	10	[2,3,5]
Hospitalised					
Work days lost					
0–4		3.17	3.17	5.04	Assumption
5–14		4.22	4.22	4.79	Assumption
15–44		5.67	5.67	6.54	Assumption
45–64		8.24	8.24	7.47	Assumption
Cost of a work day lost					
0–15	30				[25]
16–17	15				[25]
18–20	23				[25]
21–24	32				[25]
25–29	51				[25]
30–39	61				[25]
40–49	63				[25]
50–59	52				[25]
60–64	24				[25]
Household expenditures					
0–15		15	–	–	[2,24,26]
16+		35	–	–	[2,24,26]

*Reference numbers in square brackets.
†Dr Elizabeth Miller (personal communication).

consultations. For the *catch-up* and the susceptible *adolescent* programmes, it is assumed that each susceptible that is targeted is vaccinated at an additional cost of £10 over that of an infant course to cover the cost of a practice nurse consultation[19] and extra administration costs. For the *catch-up* and *adolescent strategies*, only children with negative or uncertain history of varicella are vaccinated. In our base case scenario, the sensitivity and specificity of determining a person's varicella history at 11 years was estimated to be 97% and 70% respectively.[3] This is varied in the sensitivity analysis.

Indirect costs

There are no published estimates of absenteeism caused by chickenpox in the UK, although estimates exist from other industrialised countries.[2 3 5 22–24] The average number of work-days lost per case of varicella that does not require hospitalisation was taken from the average value from studies conducted in European countries,[3 5 23] taking into account the proportion of parents who both work. For adults with varicella an estimate of 5.7 days off work was used.[2 3 5] Since there are no published estimates of absenteeism caused by zoster, the

Table 3 Current burden of varicella and zoster

	Varicella		Zoster	
	Base	(90% CrI)	Base	(90% CrI)
Health outcomes				
Cases	651000		189000	
PHN cases			26000	(25000 to 27000)
GP visits	384000	(308000 to *)	277000	
Hospitalisations	2200	(* to 2700)	2100	(* to 3500)
Deaths	20	(19 to 26)	37	(30 to 48)
Life years lost	900	(800 to 1200)	400	(400 to 600)
QALYs lost	3500	(1900 to 4700)	14400	(12100 to 24000)
Costs (£m)				
Varicella				
GP visits and VZIG	10	(7 to 10)	16	(14 to 18)
Hospitalisation	3	(3 to 4)	6	(7 to 13)
Work loss and household expenditures	41	(31 to 60)	146	(119 to 183)
Total	54	(41 to 74)	169	(140 to 214)

*Base case is the minimum or maximum value of the parameter's distribution.

Table 4 Eighty year discounted (3%) varicella and zoster health outcomes and costs saved from the various immunisation options

	Infant		Catch-up		Adolescent	
	Base	(90% CrI)	Base	(90% CrI)	Base	(90% CrI)
Health outcomes avoided						
Varicella						
Cases (millions)	14.6		15.7		1.9	
GP consultations (millions)	8.0	(6.6 to *)	8.7	(7.1 to *)	1.5	(1.0 to *)
Hospitalisations (thousands)	46.9	(* to 58.6)	51.9	(* to 65.3)	10.5	(* to 12.6)
Deaths	22	(−23 to 126)	199	(109 to 296)	128	(111 to 210)
Life-years saved (thousands)	14.2		17.4		7.4	
QALYs saved (thousands)	80.2		88.5		18.6	
Zoster						
Cases (millions)	−0.6		−0.7		−0.1	
GP consultations (millions)	−1.1		−1.3		−0.1	
Hospitalisations (thousands)	−15.5	(−31.1 to *)	−18.4	(−37.5 to *)	−1.5	(−2.9 to *)
Deaths	−444	(−550 to −336)	−526	(−650 to −393)	−41	(−51 to −31)
Life-years saved (thousands)	−4.1		−4.9		−0.4	
QALYs saved (thousands)	−134.6		−145.7		−11.0	
Overall VZV disease						
Life-years saved (thousands)	10.0	(7.7 to 16.0)	12.5	(11.2 to 21.5)	7.0	(6.0 to 11.3)
QALYs saved (thousands)	−54.4	(−155.6 to −44.1)	−67.2	(−186.9 to −40.6)	7.6	(−1.0 to 13.2)
Costs (£million)						
Vaccine costs	524	(405 to 644)	698	(557 to 863)	183	(138 to 240)
Direct medical costs prevented						
GP consultations	134	(88 to 146)	141	(90 to 152)	30	(17 to 31)
Hospitalisations	−5	(−72 to −1)	−10	(−84 to −4)	10	(5 to 13)
VZIG	18		23		11	
Total NHS costs prevented	147		154		52	
Work loss and household expenditures prevented	111	(−83 to 673)	271	(11 to 849)	293	(201 to 355)
Total societal costs prevented	258		425		344	

A minus sign implies extra cases or costs.
*Base case is the minimum or maximum value of the parameter's distribution.

number of days off work was assumed to be the average age specific duration of disease multiplied by the proportion of workdays in a week.

A

B
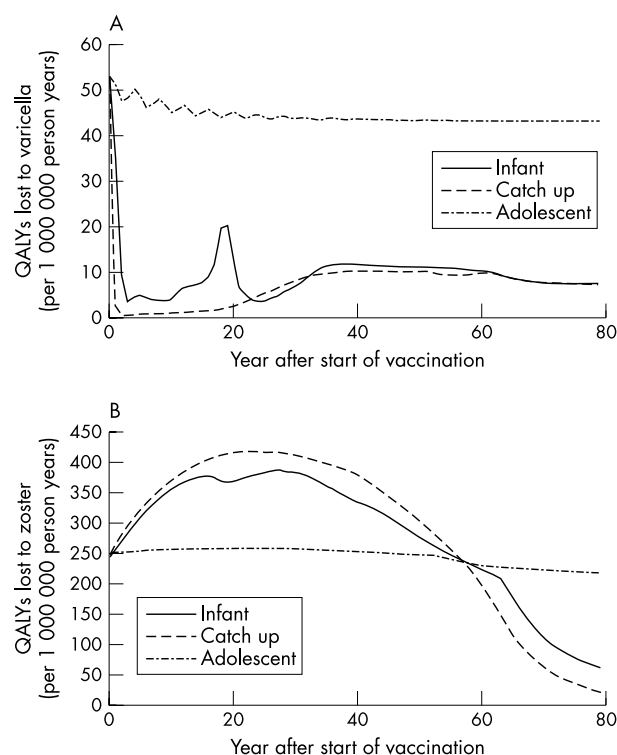
Figure 1 Estimated undiscounted QALYs lost due to (A) varicella and (B) zoster over time following the introduction of vaccination (at year 0) for different vaccine strategies (90% coverage, base case).

Work loss from hospitalised cases due to varicella and zoster was assumed to be twice the average age specific length of stay multiplied by the proportion of workdays in a week to take into account pre- and post-hospitalisation work loss.

To calculate the average cost of work loss arising from childhood cases of chickenpox and shingles, the average period of adult absence was multiplied by the average daily female wage in 25–34 year olds (weighted by the proportion in full and part time employment and inflated by rise in average earnings).[25] For adult cases, the average period of absence was multiplied by the age specific average daily wage. It was assumed that there were no work loss costs caused by illness in those over 65 years of age. Household expenditures (for example, non-prescription medications and babysitting) were based on literature from North America,[2 24 26] since no published data exists for the UK.

Sensitivity analysis

The sensitivity of the results to variation in input parameters was explored by performing a probabilistic multivariate sensitivity analysis (uncertainty analysis). Input parameters were assigned probability distributions and combinations of these parameter values were drawn using Latin hypercube sampling, assuming that they are independent of each other. For each vaccination scenario, the model was run 1000 times to generate distributions of outcome variables using @risk version 4 (Palisade Corporation, New York) running within Microsoft Excel. The parameter values and the assumed input distributions are given in the appendix. All input distributions were assumed to be triangular. Results are presented with 90% credibility intervals (C$_r$I), which show the 5th and 95th centiles of the outcome distributions. Univariate sensitivity analyses, in which parameters were varied one at a time, holding other parameter values at the base case level, were also performed.

Table 5 Univariate sensitivity analysis to key parameters—health provider perspective

	Infant	Catch-up	Adolescent
Base case	QALY Loss*	QALY Loss	£17673
Vaccine and epidemiological parameters			
Vaccine efficacy			
Best case	QALY LOSS	QALY LOSS	£24755
Worst case	£11327	£10181	£8172
Vaccine coverage			
50% infants, 50% children	QALY LOSS	QALY LOSS	£22841
95% infants, 90% children	QALY LOSS	QALY LOSS	£16837
Physician visits per case of varicella			
Lower bound 90% CrI†	QALY LOSS	QALY LOSS	£19566
Upper bound 90% CrI†	QALY LOSS	QALY LOSS	£17717
Rate of hospitalisation and length of stay			
Any ICD field	QALY LOSS	QALY LOSS	£18021
Summary outcomes			
Case fatality ratio of varicella			
Lower bound 90% CrI†	QALY LOSS	QALY LOSS	£21126
Upper bound 90% CrI†	QALY LOSS	QALY LOSS	£11129
Case fatality ratio of zoster			
Lower bound 90% CrI†	QALY LOSS	QALY LOSS	£17454
Upper bound 90% CrI†	QALY LOSS	QALY LOSS	£17801
QALY of varicella			
Lower bound 90% CrI†	QALY LOSS	QALY LOSS	£46323
Upper bound 90% CrI†	QALY LOSS	QALY LOSS	£9582
QALY of zoster			
Lower bound 90% CrI†	QALY LOSS	QALY LOSS	£12630
Upper bound 90% CrI†	QALY LOSS	QALY LOSS	QALY LOSS
Costs			
Cost per vaccine course			
−25% base case	QALY LOSS	QALY LOSS	£13081
+25% base case	QALY LOSS	QALY LOSS	£22266
Cost per consultation			
−25% base case	QALY LOSS	QALY LOSS	£18680
+25% base case	QALY LOSS	QALY LOSS	£16667
Cost per inpatient day			
−25% base case	QALY LOSS	QALY LOSS	£18004
+25% base case	QALY LOSS	QALY LOSS	£17306
Prior history of varicella			
Sensitivity			
90%		QALY LOSS	£19047
99%		QALY LOSS	£11048
Specificity			
50%		QALY LOSS	£28058
80%		QALY LOSS	£14463
Model and methodological assumption			
Duration of immunity to zoster after exposure to VZV			
7 years (lower bound 95% CI)	£9396	£10449	£7679
11 years (lower bound 75% CI)	QALY LOSS	QALY LOSS	£11421
41 years (upper bound 95% CI)	QALY LOSS	QALY LOSS	£31258
Discount rate			
Benefits 6%, costs 6%	QALY LOSS	QALY LOSS	£74511
Benefits 3%, costs 6%	QALY LOSS	QALY LOSS	£11049
Benefits 0%, costs 6%	£6249	£16933	£1579
Benefits 0%, costs 3%	£10214	£23289	£2521
Benefits 0%, costs 0%	£19327	£16511	£5228
Time scale			
30 years	QALY LOSS	QALY LOSS	£29988

*QALY loss: negative benefit of vaccination.
†90% CrI of the distribution described in table A1.

RESULTS

Current burden of varicella and zoster

The overall burden of VZV related disease is substantial (table 3). The predicted 651 000 cases of varicella per year in England and Wales result in an estimated 384 000 physician visits, 2200 hospitalisations, and 20 deaths. Comparatively, there are annually an estimated 189 000 cases of zoster, and 277 000 physician visits, 2100 hospitalisations, and 37 deaths. The estimated overall QALYs lost due to varicella and zoster is 18 000 (90% C_rI 14 000–29 000), 80% of which are due to zoster.

The overall societal cost of VZV related disease in England and Wales is estimated to be £223m annually (90% C_rI, £181m–£288m; table 3), 76% (£169m) of which are attributable to zoster. Most of societal costs (£175m, 78%) are due to

work loss, £12m are due to household expenditures, and £35m are due to direct medical costs. Of the annual £35m VZV is estimated to cost the NHS, £13m is due to varicella (£20 per case) and £22m is due to zoster (£116 per case).

Cost-utility analysis

The model predicts that although the overall burden of varicella will significantly be reduced following mass infant vaccination, these benefits will be offset by a rise in zoster morbidity, which will last more than 60 years (see fig 1 and Brisson and colleagues[11]). Table 4 shows the predicted health outcomes prevented by vaccination. Under base case assumptions (90% coverage and 3% discount rate), *infant* vaccination would prevent 15m varicella cases over 80 years and generate an extra 1m cases of zoster, resulting in an overall loss of
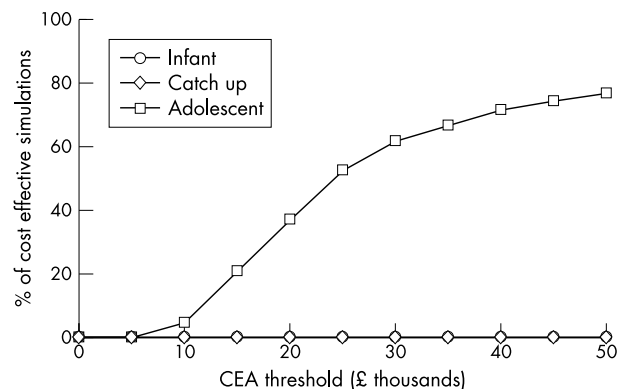
Figure 2 The proportion of simulations that would be deemed cost-effective for different threshold values of cost per QALY gained (vaccine efficacy and duration of immunity to zoster after exposure to VZV are held constant at base case values).

54 000 discounted QALYs. The loss of QALYs is greater for the *catch-up strategy* (table 4) as the increase in zoster incidence is greater (fig 1). The projected discounted costs of the *infant* and *catch-up* programmes are £524m (90% C_rI, £405m–£644m) and £698m (90% C_rI, £557m–£863m) respectively, which is estimated to avoid £147m and £154m in direct medical costs (table 4). Thus, under base case assumptions, infant vaccination is estimated to produce an overall increase in morbidity (as measured by discounted QALYs) and to result in a net cost from the NHS perspective. Other catch-up strategies, such as vaccination of 11 year olds for the first 10 years of vaccination were investigated. Although less costly than the *catch-up strategy* presented here, such a strategy is estimated to result in a similar loss of QALYs.

Routine vaccination of 11 year olds (*adolescent strategy*) with 80% coverage reduces varicella cases by 2m and results in zoster increases of less than 0.1m over 80 discounted years (table 4), resulting in 8000 QALYs saved. This is estimated to result in savings of £52m in direct medical costs over 80 years, but at a cost of £183m (90% C_rI, £138m–£240m) (table 4). Thus, under base case assumptions, the cost-utility ratio for *adolescent vaccination* is estimated to be approximately £18 000 per QALY gained.

Of the strategies investigated, only the *adolescent strategy* is cost saving from the societal perspective (present value of 161m over 80 years; table 4). The *infant* and *catch-up strategies* are estimated to cost £266m and £273m over 80 discounted years respectively (table 4). The 90% C_rI of these values are wide (table 4) since little is known of the indirect costs of zoster.

Sensitivity analysis
Univariate sensitivity analysis
Table 5 shows the sensitivity of results to changes in the key parameters. The cost-utility of *infant* and *catch-up* vaccination is most sensitive to vaccine efficacy and the duration of immunity to zoster after exposure to VZV. If vaccine efficacy is poor (worst case scenario) or duration of immunity to zoster after exposure to VZV is seven years (lower bound of the 95% CI estimated by Brisson and colleagues[9]), then *infant* and *catch-up* vaccination are estimated to cost approximately £10 000 per QALY saved. The cost-effectiveness of infant varicella vaccination is also sensitive to the choice of discount rate and time frame of the analysis. Because zoster morbidity will eventually decline after 60 years,[9–11] lower discount rates for benefits and longer time frames of analysis will cause varicella vaccination to be more cost-effective (table 5). Infant varicella vaccination remains highly cost-ineffective for changes in all other key parameters (table 5).

The results of the *adolescent* programme are sensitive to changes in parameter values. However, most scenarios cost less than £25 000 per QALY saved. Parameters with the greatest impact on results are the QALYs lost due to varicella and zoster and the discount rate.

Multivariate sensitivity analysis
Figure 2 summarises the results of the multivariate (probabilistic) sensitivity analyses. Figure 2 can be interpreted as showing the probability that each of the programmes would be deemed cost-effective for alternative values of society's maximum willingness to pay for a QALY gained under base case assumptions regarding boosting following exposure to varicella.[9] The results suggest that infant vaccination (with or without a catch-up programme) would be highly unlikely to be cost-effective. On the other hand, vaccination of susceptible 11 year olds is cost-effective under many acceptable criteria.

DISCUSSION
Conclusions regarding the cost-effectiveness of infant varicella vaccination (with and without catch-up) rest heavily on the impact it will have on the incidence of zoster. The increase in zoster following vaccination is dependent on vaccine effectiveness at preventing varicella and the length of time exposure to VZV protects against zoster.[9–11] If duration of immunity to zoster after exposure to VZV is more than 10 years (lower bound of the 85% CI[9]) and vaccination is effective at preventing varicella (as appears to be the case[27]), then universal infant strategies are unlikely to be cost-effective and are likely to produce an increase in overall morbidity (that is, losses of QALYs). This conclusion is robust to changes in all other key variables investigated here.

It should be noted that if time preference is such that short and long term benefits are valued equally (zero or very low discount rate), then infant varicella vaccination would be worthwhile, since after 60 years a reduction in zoster cases will occur, provided that vaccine recipients are less likely to develop zoster than individuals who have acquired natural infection.[9–11]

Under all scenarios investigated, *adolescent* vaccination is the most cost-effective option from the health provider's perspective because, per vaccinee, there is a larger reduction of serious disease than for the infant programmes. Furthermore, it is the safest option since it has little effect on the age at infection and incidence of zoster. However, the cost-effectiveness of this strategy depends on the accuracy of the QALY measures for varicella and zoster.

Strengths and limitations of the analysis
The analysis presented here expands on previous analyses in three major areas. Most importantly we include the possible effect of zoster on the cost-effectiveness of varicella vaccination using a dynamic mathematical model[11] parameterised from recent data.[9] Secondly, we use cost per QALY as the main outcome measure. Using QALYs, instead of life-years gained, as most studies have done,[1–6] is the more appropriate option since the main aim of varicella vaccination is to reduce VZV morbidity (VZV causes little mortality). Finally, like Lieu and colleagues,[2] Coudeville and colleagues,[5] and Brisson and Edmunds,[6] we take into account herd immunity effects such as increases in the average age of varicella that would be expected to occur after vaccination.

The main limitation of the cost-effectiveness analysis presented here is the lack of data on the indirect costs due to varicella and zoster. Furthermore, the mathematical model has two main limitations. First, it has a simplified age structure in the elderly, which results in an underestimate of the overall burden of zoster in this age group.[17] Hence, results may overestimate the cost-effectiveness of varicella vaccination. Finally, a better understanding of the mechanisms that

lead to the development of shingles is needed to improve accuracy of model predictions.

At present there are no preventative measures against zoster. Vaccine trials are underway in the USA to determine whether immunisation of older adults will reduce the frequency and/or severity of zoster and post-herpetic neuralgia. If these are successful, then the optimal strategy may be to vaccinate both children and adults to prevent varicella and zoster, respectively.

Conclusion

Adolescent vaccination is the safest and most cost-effective strategy. Routine infant varicella vaccination is unlikely to be cost effective and may produce an increase in overall morbidity due to a rise in cases of zoster.

APPENDIX

Table A1 presents input values for the multivariate analysis.

Table A1 Input values for the multivariate analysis

Parameter		Minimum (source)		Maximum (source)	
% cases consult GP*					
Varicella	0–4	36%	RCGP	48%	RCGP
	5–14	26%	RCGP	45%	RCGP
	15–44	30%	RCGP	72%	RCGP
	45–64	48%	RCGP	100%	RCGP
	65+	57%	RCGP	100%	RCGP
Hospitalisations per case					
Varicella†	0–4	0.4%	HES	0.5%	HES
	5–14	0.1%	HES	0.2%	HES
	15–44	0.6%	HES	0.8%	HES
	45–64	1.4%	HES	1.9%	HES
	65+	3.1%	HES	5.8%	HES
Zoster†	0–4	1.1%	HES	1.4%	HES
	5–14	0.7%	HES	1.0%	HES
	15–44	0.5%	HES	0.8%	HES
	45–64	0.6%	HES	1.2%	HES
	65+	2.3%	HES	5.0%	HES
Length of stay (days)					
Varicella†	0–4	2.2	HES	2.7	HES
	5–14	3.0	HES	3.6	HES
	15–44	4.0	HES	4.8	HES
	45–64	5.8	HES	7.9	HES
	65+	10.6	HES	15.8	HES
Zoster†	0–4	3.5	HES	5.3	HES
	5–14	3.4	HES	3.4	HES
	15–44	4.6	HES	6.1	HES
	45–64	5.2	HES	8.7	HES
	65+	13.5	HES	17.4	HES
Case fatality					
Varicella‡	0–4	0.0006%	ONS	0.0017%	ONS
	5–14	0.0004%	ONS	0.0006%	ONS
	15–44	0.0063%	ONS	0.0167%	ONS
	45–64	0.0733%	ONS	0.1011%	ONS
	65+	0.3880%	ONS	0.8536%	ONS
Zoster‡	0–4	0.0000%	ONS	0.0000%	ONS
	5–14	0.0000%	ONS	0.0068%	ONS
	15–44	0.0000%	ONS	0.0086%	ONS
	45–64	0.0012%	ONS	0.0035%	ONS
	65+	0.0403%	ONS	0.0831%	ONS
PHN per zoster case					
	0–4	0.0%	[17]	0.0%	[17]
	5–14	0.0%	[17]	1.7%	[17]
	15–44	2.6%	[17]	4.9%	[17]
	45–64	10.0%	[17]	11.9%	[17]
	65+	28.7%	[17]	33.4%	[17]
Duration of PHN		339	[17]	781	[17]
QALY lost per case					
Varicella	0–14	0.01%	Study§	0.64%	Study§
	15+	0.32%	Study¶	1.02%	[17]††
Zoster		0.85%	[17]**	1.67%	[17]††
Cost estimates		−25% Base		+25% Base	
Reported history of chickenpox					
Sensitivity		90%	[28]	99%	Assumption
Specificity		50%	[29]	80%	[4]

*Minimum is minimum number of varicella consultations observed in the RCGP data in a year between 1991 and 2000. Maximum is maximum number of varicella consultations in a year between 1991 and 2000.
†Minimum is varicella or zoster in the first diagnostic field (Hospital Episode Statistics, HES). Maximum is varicella or zoster in any of the diagnostic fields.
‡Minimum is minimum case fatality in a year between 1991 and 2000 (observed in ONS mortality statistics). Maximum is maximum case fatality in a year between 1991 and 2000.
§Maximum and minimum values of the triangular distribution which fitted best the QALY values obtained from 42 parents of children with prior history of chickenpox.
¶Average of QALY value obtained from 10 specialist registrars working at CDSC using the HUI2 generic health status index.
**QALY value for mild zoster.
†† QALY value for severe zoster.

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